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Original Article

Persistence of non-vitamin K antagonist oral anticoagulant use in Japanese patients with atrial fibrillation: A single-center observational study

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ABSTRACT

Background: Non-vitamin K antagonist oral anticoagulants (NOACs) show a favorable balance between efficacy and safety compared with warfarin for patients with non-valvular atrial fibrillation (NVAF). In "real-world" practice, however, NOAC adherence and persistence among patients are not clear. The aim of this study is to evaluate NOAC and warfarin persistence in Japanese patients with NVAF who newly started these drugs.

Methods: We retrospectively studied 401 patients with NVAF who had newly started NOACs during the first 18 months after our hospital adopted their use (197 dabigatran, 107 rivaroxaban, 102 apixaban) and 200 patients with NVAF who had newly started warfarin during the same period. The endpoint was drug discontinuation for each drug.

Results: During the follow-up period (up to a maximum of 24 months), 113 (28%) patients who had newly started NOACs and 33 (17%) patients who had newly started warfarin discontinued the drug. The persistence rates of patients prescribed NOACs was lower than that of patients prescribed warfarin at 3, 6, and 12 months (85% versus 93%, 79% versus 88%, and 70% versus 82%, respectively). One-tenth of patients who had newly started NOACs discontinued the drug by their own decision. Drug adverse events, worsening renal dysfunction, and patient desire were the major causes of NOAC discontinuation.

Conclusions: The rate of persistence of prescribed NOACs was significantly lower than that of warfarin in Japanese patients with NVAF.

1. Introduction

Atrial fibrillation (AF) is the most clinically prevalent tachyarrhythmia [1,2]. AF is a potential risk factor for stroke, and AF-associated strokes are often severe, resulting in disability or death [3–6]. Anticoagulant therapy with the vitamin K antagonist warfarin reduces the risk of AF-related stroke [7]. However, warfarin has been underused for at-risk patients with AF in clinical practice [8,9]. Additionally, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study showed that 26.3% of 4188 patients newly starting warfarin for AF discontinued therapy in the first year [10]. In a real-world setting, adherence to oral anticoagulation therapy is important for the prevention of stroke in at-risk patients with AF, because clinical outcomes such as mortality, stroke, and cardiovascular events are strongly dependent on the quality of anticoagulation and rate of warfarin discontinuation [11,12].

Recently, several non-vitamin K antagonist oral anticoagulants (NOACs) have been developed. Landmark phase 3 randomized clinical trials (RCTs) compared NOACs with warfarin and demonstrated that NOACs are at least as safe and effective as warfarin to prevent stroke/systemic embolisms in patients with non-valvular AF (NVAF) [13–17]. Current AF guidelines based on this evidence recommend the risk stratification and use of NOACs [18–21].

The average rates of adherence in RCTs can be remarkably high, owing to the attention study patients receive and to the selection of the patients [22]. In "real-world" practice, however, it is not clear whether the adherence and persistence of patients to NOACs are better than those to warfarin in patients with NVAF. Moreover, no

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reports have focused on this issue in Japanese patients with NVAF taking NOACs. The aim of this study was to evaluate NOAC persistence and to compare it with warfarin persistence in Japanese patients with NVAF who newly started these drugs.

2. Materials and methods

2.1. Subjects

We retrospectively conducted a cohort study of patients with NVAF who had newly started NOACs during the 18 months after the adoption of these new drugs in our hospital. All patients were treated in the Departments of Cardiology and Neurology at Tokyo Women's Medical University Hospital. This study included 192 consecutive patients who started dabigatran between March 2011 and September 2012, 107 consecutive patients who started rivaroxaban between June 2012 and November 2013, 102 consecutive patients who started apixaban between April 2013 and September 2014, and as reference, 200 consecutive patients who started warfarin between March 2011 and September 2012. To identify patients who were prescribed NOACs and warfarin, we first searched automated prescription databases. Then, we confirmed each patient's diagnosis of AF by checking his/her medical records. We excluded patients with valvular heart disease, concurrent hyperthyroidism, or hemodialysis, as well as those without risk factors for stroke. Valvular heart disease was defined as moderate or severe mitral stenosis and mild rheumatic mitral stenosis according to angiographic, hemodynamic, or echocardiographic results, or a history of valvular surgery, including valvular repair or replacement. This study was approved by the institutional review board of Tokyo Women's Medical University (approval number 2887-R).

2.2. Clinical characteristics

Data on patient age, sex, traditional risk factors, underlying disease, and concomitant medications were obtained from medical records and laboratory data. Creatinine clearance was calculated using the Cockcroft–Gault formula [23]. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, a diastolic blood pressure $\geq$ 90 mmHg, or a history of treatment for hypertension. Diabetes mellitus previously diagnosed by a physician was defined by treatment with hypoglycemic agents or was indicated by poor glycemic control (defined as a glycohemoglobin A1c $\geq$ 6.5%). Coronary artery disease was defined based on positive stress test results, coronary angiography demonstrating at least 75% of stenosis, coronary spastic angina documented by an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Heart failure was defined according to the American College of Cardiology/American Heart Association criteria [24]; of the patients included, those who had heart failure were designated as having stage C (current or prior symptoms of heart failure) or stage D (refractory heart failure).

The $CHADS_2$ score (congestive heart failure, hypertension, age $\geq$ 75, diabetes, stroke [doubled]) and the CHA_2DS_2-VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age $\geq$ 75 [doubled], diabetes, stroke [doubled] – vascular disease, age 65–74, and sex category [female]) were used to measure stroke risk.

2.3. Follow-up

Follow-up data were obtained at routine or additional visits at our institution. The patients were followed until the end of the follow-up period (24 months after the initiation of each drug, except for apixaban, where the follow-up period was 22 months; for dabigatran and warfarin, the follow-up period was until March 2013; for rivaroxaban, this was until May 2014; and for apixaban, this was until January 2015) or until discontinuation of the drug, loss to follow-up, or death. Information concerning deceased patients was obtained from medical records, family members, the patients' general practitioners, and the hospitals to which they had been admitted. In patients who started warfarin, we also collected prothrombin time-international normalized ratio (PT-INR) data.

2.4. Outcomes

Cessation of drugs was defined as discontinuation of the prescribed drug, and physician's mention of drug cessation on the medical record. All drug cessations were reviewed from medical records, and the reasons for cessation were also obtained. Temporary discontinuation for specific reasons such as surgery was not considered as drug cessation. The occurrence of thromboembolic and bleeding events was validated through the medical records review by three investigators (M.N., T.S., and T.N.). Thromboembolic events included fatal or nonfatal ischemic stroke, transient ischemic attack (TIA), or other systemic embolism. Ischemic stroke was defined as the sudden onset of a new focal neurological deficit lasting more than 24 h that could not be explained by other causes. TIA was diagnosed when the neurological deficit lasted less than 24 h. Computed tomography or magnetic resonance imaging was performed in all patients. Other systemic embolisms were diagnosed using computed tomography, angiography, or thrombectomy, and were based on the absence of underlying atherosclerosis in the affected artery. Major bleeding events were defined as intracranial hemorrhage observed by imaging or surgery, intraocular hemorrhage leading to a substantial loss of vision, or gastrointestinal bleeding or another severe hemorrhage that was fatal or required endoscopic hemostasis, surgical intervention, hospital admission, or blood transfusion. For patients who were admitted to other hospitals due to these events and were not subsequently observed at our hospital, the information was obtained from those hospitals. A neurologist (T.N.) also reconfirmed the diagnoses of stroke, TIA, and intracranial hemorrhage in these patients.

2.5. Statistical analysis

Summary data are presented either as the mean and standard deviation (SD) or as the numbers of patients. Baseline clinical data were compared between groups with and without depression using the Student's *t*-test and the Mann–Whitney *U*-test. Categorical variables were subjected to chi-square analysis. Time in the therapeutic range (TTR) was calculated using the Rosendaal linear interpolation method [25], which is a linear interpolation of consecutive PT-INR values that calculates the percentage of time that the PT-INR is below, within, or above the target therapeutic range (1.50–2.49). The rates of events were compared between individual groups using the chi-square test. The cumulative rates of persistence for the prescribed drugs were calculated using the Kaplan–Meier method. Differences in persistence rates were compared using the log rank test. P values < 0.05 were considered significant. Data analyses were performed using SPSS statistical software (version 11.01, SPSS Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics

The patients' baseline characteristics are shown in Table 1. There were no differences in age or gender between users of NOACs and warfarin. The proportions of heart failure and diabetes mellitus in

Table 1
Baseline characteristics of the patients.

	Dabigatran ($n=192$)	Rivaroxaban ($n=107$)	Apixaban ($n=102$)	Warfarin ($n=200$)
Age, years	70 ± 9	70 ± 10	70 ± 10	68 ± 13
Female	50 (26%)	34 (32%)	43 (42%)	65 (33%)
Body weight (kg)	64 ± 11	62 ± 14	62 ± 14	62 ± 13
CCr (ml/min)	72 ± 23	67 ± 26	66 ± 25	71 ± 31
Heart failure	34 (18%)	10 (9%)*	20 (20%)	37 (19%)
Hypertension	123 (64%)	67 (63%)	64 (63%)	133(67%)
Diabetes mellitus	56 (29%)	24 (22%)*	35 (34%)	68 (34%)
Previous stroke/TIA	91 (47%)**	28 (26%)	27 (27%)	48 (24%)
Coronary artery disease	44 (23%)	11 (10%)	15 (15%)	33 (17%)
$CHADS_2$ score				
0	28 (15%)	10 (9%)	11 (10%)	32 (16%)
1	35 (18%)	35 (33%)	27 (26%)	45 (23%)
2–6	129 (67%)	62 (58%)	64 (63%)	123(62%)
CHA_2DS_2-VASc score				
0	9 (5%)	5 (5%)	3 (3%)	17 (9%)
1	22 (11%)	13 (12%)	12 (12%)	25 (13%)
2	27 (14%)	16 (15%)	22 (22%)	37 (19%)
3	34 (18%)	34 (32%)*	19 (19%)	40 (20%)
4–9	100 (52%)*	39 (36%)	46 (45%)	81 (41%)
Dose (mg daily) of NOACs				
	300 mg	15 mg	10 mg	
	56 (29%)	40 (28%)	66 (65%)	
	220 mg	10 mg	5 mg	
	128 (67%)	66 (62%)	36 (35%)	
	150 mg	5 mg		
	8(4%)	1 (1%)		

The values are expressed as n (%) or mean ± SD.
AF, atrial fibrillation; CCr, creatinine clearance; NOACs, non-vitamin K antagonist oral anticoagulants; TIA, transient ischemic attack.
$CHADS_2$ = cardiac failure, hypertension, age ≥ 75 years, diabetes, previous stroke or TIA (doubled).
CHA_2DS_2-VASc = congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/TIA/thromboembolism (doubled), vascular disease, age 65–74 years, female sex.

* $p < 0.05$ compared with warfarin.
** $p < 0.01$ compared with warfarin.

patients prescribed rivaroxaban were lower than those in patients prescribed warfarin. However, the proportion of previous stroke/TIA in patients prescribed dabigatran was higher than that in patients prescribed warfarin. The distribution of $CHADS_2$ scores was not different between each NOAC and warfarin, but the proportion of patients with CHA_2DS_2-VASc ≥ 4 in patients prescribed dabigatran was higher than that in patients prescribed warfarin.

3.2. NOAC and warfarin persistence

During the follow-up period, 113 (28%) of 401 patients who had newly started NOACs discontinued the drug, and 33 (17%) of 200 patients who had newly started warfarin discontinued the drug. Kaplan–Meier curves for NOAC and warfarin persistence are shown in Fig. 1. There was a significantly higher rate of NOAC discontinuation compared with warfarin discontinuation within the first year of treatment. As Fig. 2 shows, patients prescribed warfarin were more likely than those in the 3 NOAC groups to show drug persistence. The rate of dabigatran discontinuation was significantly higher than that of warfarin discontinuation within the first year of treatment (hazard ratio 2.19, 95% confidence interval: 1.44–3.34, $P < 0.01$).

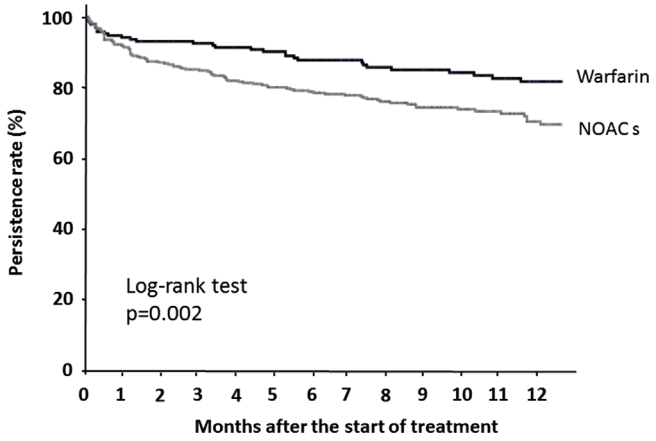

Fig. 1. Kaplan–Meier curves for the persistence of NOACs ($n=401$) and warfarin ($n=200$) in non-valvular atrial fibrillation patients. NOAC, non-vitamin K antagonist oral anticoagulant.

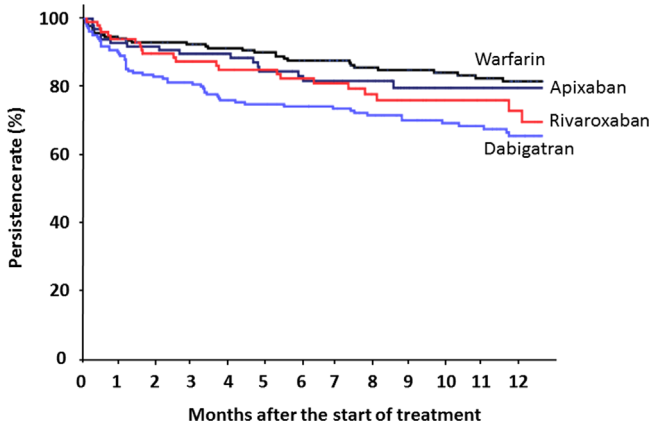

Fig. 2. Kaplan–Meier curves for the persistence of each NOAC (dabigatran $n=197$, rivaroxaban $n=107$, apixaban $n=102$) and warfarin ($n=200$) in non-valvular atrial fibrillation patients. NOAC, non-vitamin K antagonist oral anticoagulant.

Table 2
Discontinuation of drugs and causes of cessation.

Event	Dabigatran ($n=192$)	Rivaroxaban ($n=107$)	Apixaban ($n=102$)	Warfarin ($n=200$)
Discontinuation	65 (34%)	30 (28%)	18 (18%)	33 (17%)
By the patient's own decision	5	4	1	3
Causes of cessation				
Adverse events	27 (42%)	11 (37%)	9 (50%)	6 (18%)
Gastrointestinal symptoms	8	2	0	1
Bleeding	3	5	1	1
Abnormal laboratory data	8	1	3	3
Other	8	3	5	1
Worsened renal function	6 (9%)	0	0	0
Patient desire	6 (9%)	10 (33%)	2 (11%)	3 (9%)
Poor control of PT-INR				2 (6%)
Maintenance of sinus rhythm	6 (9%)	3 (10%)	3 (17%)	14 (42%)
Other	19 (29%)	6 (20%)	4 (22%)	8 (24%)

PT-INR, prothrombin time-international normalized ratio.

3.3. Discontinuation of drugs and cause of cessation

Approximately one-tenth of patients who discontinued the drug did so of their own accord without consulting a doctor or pharmacist (Table 2). Adverse events, including gastrointestinal symptoms

and bleeding during anticoagulant therapy, were the most common reason for discontinuing NOACs. Among patients prescribed dabigatran, which is highly excreted by the kidney, worsened renal function was also an important cause for discontinuation. Patient desire was the next most common cause. The patients who discontinued anticoagulation due to maintenance of sinus rhythm partially included post-AF ablation patients with low risk. Other causes included cost, number of administrations, two-week limit on the prescription period, and switching from NOACs to warfarin or from warfarin to NOACs for surgical/interventional procedures (Table 2).

3.4. Outcomes

Incidences of thromboembolic and major bleeding events were not different between patients prescribed NOACs and those prescribed warfarin (Table 3). The mean TTR was 53% during the initiation and maintenance phases of warfarin therapy. Two patients with dabigatran experienced ischemic stroke/TIA after the discontinuation of the drug by their own decision.

Antithrombotic treatment after the discontinuation of drugs is shown in Table 4. Of the patients who discontinued NOACs, half received warfarin and one-fifth received a NOAC, mostly another NOAC. One-fourth of the patients who discontinued warfarin received NOACs. However, one-fifth of patients who discontinued NOACs and three-fourths of patients who discontinued warfarin did not receive any subsequent antithrombotic therapy.

4. Discussion

Our study in patients with NVAF who had newly started NOACs or warfarin revealed the following findings: (1) patients prescribed NOACs had a significantly lower drug persistence rate within one year after the start of the drug than did patients prescribed warfarin; (2) one-fourth of patients who had newly started NOACs discontinued the drug, and one-tenth of these patients discontinued it by their own decision without consulting a doctor or pharmacist; (3) adverse events, worsening renal dysfunction, and patient desires were the major causes of NOAC discontinuation; (4) incidences of thromboembolism and major bleeding were not different for NOACs and warfarin; (5) half of the patients who discontinued NOACs received warfarin after the discontinuation, but one-fifth of patients did not receive any subsequent antithrombotic drugs.

4.1. NOAC persistence

In clinical practice, we use NOACs for several patients with NVAF, who are quite different from the patients selected in RCTs. Drug persistence is important for the success of anticoagulant therapy. It is possible that non-adherence to or discontinuation of NOACs will influence clinical outcome in these patients. The subanalysis of Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) showed that the risk of stroke or systemic embolism was similar with rivaroxaban or warfarin in patients with AF who temporarily or permanently discontinued anticoagulation [26]. A recent national cohort of 5376 patients with NVAF who started on dabigatran at all Veterans Affairs hospitals in the US showed that lower adherence was associated with increased risk for combined all-cause mortality and stroke [27]. The propensity-matched analysis of that cohort study also showed that the persistence rate of patients prescribed dabigatran was higher than that of patients prescribed warfarin at 6, 9, and 12 months, analyzed with a 60-day permissible medication gap (71.8% versus 53.3%, 66.9% versus 44.0%, 63.3% versus 38.8%, respectively) [28]. The differences in the medical care systems, e.g., the number of regular meetings with a cardiologist for monitoring of PT-INR and dose adjustment of warfarin, between Japan and the US might partially influence the difference in warfarin persistence between that US cohort and ours. However, this factor might not influence dabigatran persistence, which does not require laboratory monitoring, and the discontinuation of dabigatran in our study was not particularly low. Although we can check the adherence to warfarin use by monitoring PT-INR, we cannot assess the adherence of NOACs, which do not require laboratory monitoring. In our study, two patients who had discontinued dabigatran by their own decision experienced ischemic stroke/TIA. This issue will arise as a new problem in the NOAC era.

Table 3
Thromboembolic and major bleeding events.

Event	Dabigatran ($n=192$)	Rivaroxaban ($n=107$)	Apixaban ($n=102$)	Warfarin ($n=200$)
Thromboembolism				
Ischemic stroke	2	2	2	2
TIA	1	0	0	0
Systemic embolism	0	0	0	0
Major bleeding				
Intracranial hemorrhage	0	0	1	2
Gastrointestinal bleeding	1	3	0	2

TIA, transient ischemic attack.

Table 4
Antithrombotic treatment after discontinuation of each NOAC and warfarin.

Treatment	Dabigatran ($n=65$)	Rivaroxaban ($n=30$)	Apixaban ($n=18$)	Warfarin ($n=33$)
Warfarin	39 (60%)	14 (47%)	8 (44%)	0
NOACs	11 (17%)	8 (27%)	3 (17%)	8 (24%)
Antiplatelet	3 (5%)	2 (7%)	1 (6%)	0
Other antithrombotic therapy	0	0	0	1 (3%)
None	11 (17%)	6 (20%)	6 (33%)	24 (72%)

NOACs, non-vitamin K antagonist oral anticoagulants.

4.2. Cause of cessation

In our study, the time to NOAC discontinuation was relatively shorter (several months) than the time to warfarin discontinuation. In most cases, discontinuation was because of the adverse events of the treatment, although these were not severe, or patient desire. In anticoagulation therapy, minor bleeding is commonly observed but does not lead to severe or serious major bleeding [29]. However, patients, especially Japanese patients, dislike experiencing side effects from drugs. Moreover, patient preference is an important factor in adherence to anticoagulation treatment. The 2014 American Heart Association/American Stroke Association guideline recommended that the selection of an antithrombotic agent should be individualized on the basis of cost, tolerability, and patient preference, as well as risk factors [30].

4.3. Differences among NOACs

To interpret our results, the drug approval time of each NOAC should be considered. Dabigatran was first approved for use as a NOAC in Japan in January 2011, prior to its approval in Europe. In August 2011, the Japanese Ministry of Health, Labour and Welfare issued a safety advisory to warn of the potential for serious adverse events with dabigatran; this safety advisory was subsequent to the death of five patients who were taking this drug, all of whom were elderly, and four of whom were suspected of having severe renal

impairment [31]. Therefore, physicians in Japan were advised to carefully monitor for signs of anemia and bleeding, and were also advised to perform renal function tests before and during the administration of NOACs. These experiences were good opportunities to allow Japanese physicians to comprehend the pharmacokinetics of NOACs, particularly their hepatic metabolism, renal excretion, and drug-drug interactions. Thereafter, many physicians began to pay attention to the indications and patient selection for NOACs, and treatment management has been good for the last 4 years. In fact, there were no differences in the incidences of thromboembolic and major bleeding events between NOACs and warfarin in our study. Therefore, the discontinuation rates of rivaroxaban and apixaban (approved in January and December 2012, respectively) might be lower than that of dabigatran.

4.4. Antithrombotic treatment after drug discontinuation

In our study, one-fourth of patients who discontinued NOACs and three-fourths of patients who discontinued warfarin did not continue with antithrombotic therapy after the discontinuation of the drug. Although the majority of these patients might have a low risk of stroke, physicians should not prescribe anticoagulants if they might have to discontinue anticoagulation therapy. Recent guidelines recommend NOACs for patients with low risk [18–21,30]. Physicians should cautiously consider the indications for anticoagulant therapy.

4.5. Adherence to NOAC treatment

Several patient-related factors, patient psychology and behavior, the medication, disease, healthcare system, medical practitioner, and patient–physician relationship affect adherence to medication [32,33]. We also need to recognize barriers to adherence. There is no single approach to ensure patient adherence, and any attempts to improve adherence must involve the patient in the decision-making process [32]. Based on our results, the following issues will be required to improve adherence of NOACs. Before physicians first prescribe a NOAC, they should give patients detailed information regarding adverse events of the drug that often occur within several months. Physicians should explain the risk of discontinuation and the necessity of consulting physicians and pharmacists if the patient is concerned about discontinuing the drug. Physicians should select the correct drug based on patient preference as well as cost and risk of stroke. Patient education and follow-up systems with pharmacists at community-dispensing pharmacies in collaboration with physicians are needed to improve the adherence and management of anticoagulant therapy in patients with AF.

4.6. Limitations

There are some limitations to this study. First, the study was a retrospective observational study, and the number of subjects was small. Additionally, treatment selection bias existed. Second, this was a single-center cohort study. The clinical characteristics of our patients might not reflect those of average patients with NVAF in Japan because our institution is a university hospital. Third, we could not detect all minor events.

5. Conclusions

There was a significantly higher rate of discontinuation within one year after the start of using NOACs compared with warfarin. To improve adherence to NOACs, further educational and management systems for patients with AF will be required.

Disclosures

Dr. Shiga received research funding from Eisai, and lecture fees from Eisai, Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi-Sankyo. Dr. Nagao received lecture fees from Boehringer Ingelheim, Bayer Healthcare, and Bristol-Myers Squibb. Dr. Murasaki received lecture fees from Eisai, Bayer Healthcare, and Daiichi-Sankyo. Dr. Hagiwara received research funding from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr. Maruyama and Ms. Naganuma have no disclosures to make.

Conflict of interest

None declared.

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